

### **3. Remarks**

Applicant's representative thanks the Examiner for the telephone interview of February 22, 2006. In this teleconference, the Examiner identified subject matter that he believed to be patentable. Applicant's representative understood this to include claims directed to methods for increasing sialylation of a protein comprising a step of culturing cells in a medium comprising N-acetylmannosamine, galactose, fructose, and mannose and claims directed to media containing these four sugars. The Examiner also suggested replacing "controlling" in the preamble of the method claims with "increasing." The Examiner also indicated that new arguments or amendments for other claims might be considered in future prosecution.

#### ***Claim Amendments***

Claims 1-43 have been cancelled without prejudice. Applicant reserves the right to pursue this subject matter in future prosecution. A new claim set has been submitted so that the claim order and dependency makes more sense. For example, in the former claim set, both method and medium claims were independent, even though the method claims did in most cases include all the limitations of a medium claim. In the new claim set, the method claims are dependent on medium claims. In addition all method claims have been amended such that the methods are methods for "increasing" the sialic acid content of the protein rather than "controlling" the sialic content of the protein. Other than these changes, the new claims are very similar to the formerly pending claims.

#### ***Claim Rejections – 35 USC § 103***

Claims 1-11 and 13-43 stand rejected as obvious over Franze et al. (US Pat. No. 6,673,575) in view of Schnarr et al. (US Pat. No. 6,274,568), Wood (US Pat. No. 6,472,175), Gu and Wang (Biotechnol. Bioeng. 58: 642-48 (1998)), or Gu and Wang (Abstracts of Papers Amer. Chem. Soc. 213(1-3): BIOT 106). Gu and Wang (1998) indicate that addition of N-acetylmannosamine (ManNAc) can increase the sialylation of a particular protein made in CHO cells. Franze et al., disclose a process for isolating a glycosylated polypeptide that includes adding to culture medium a mixture of at least two or, preferably at least three, carbohydrates. Franze et al., col. 2-3.

A prima facie case of obviousness requires (1) a suggestion in the cited references or within the knowledge in the art to modify or combine the references to achieve the claimed invention, (2) a reasonable expectation of success, (3) the disclosure of all claim limitations in the cited references. MPEP 2142. It is well settled law that the selection of a species from a large genus disclosed in a prior art reference is nonobvious. *In re Baird*, 29 USPQ2d 1550 (Fed. Cir. 1994). In *Baird*, the patent claimed “[a] flash fusible toner comprising a binder resin which is a bisphenol A polyester containing an aliphatic di[carboxylic] acid selected from the group consisting of succinic acid, glutaric acid and adipic acid.” This claim was rejected for obviousness over Knapp et al., which disclosed the polymeric esterification product of a dicarboxylic acid and a diphenol. A generic chemical formula for the dicarboxylic acid plus diphenol was disclosed, with possibilities for wide variations at five points in the generic chemical structure. Thus, Knapp disclosed a broad genus encompassing, the Court estimated, perhaps 100 million different diphenols. *Baird, supra*. Knapp also specifically recited typical dicarboxylic acids including succinic acid, glutaric acid, and adipic acid (as recited in Baird’s claim). However, the Court found that “[g]iven the vast number of diphenols encompassed by the generic diphenol formula in Knapp, and the fact that the diphenols that Knapp specifically discloses to be “typical,” “preferred,” and “optimum” are different from and more complex than bisphenol A, we conclude that Knapp does not teach or fairly suggest the selection of bisphenol A.” *Baird, supra*. Thus, the court found the claim nonobvious over Knapp et al.

The disclosure of Franze et al., like that of Knapp et al., discloses a broad genus of combinations of carbohydrates.

The carbohydrates are preferably selected from monosaccharides and disaccharides such as glucose, glucosamine, ribose, fructose, galactose, mannose, sucrose, lactose, mannose-1-phosphate, mannose-1-sulfate and mannose-6-sulfate. Nutrient media are for example suitable which contain glucose or/and mannose or/and galactose. Particularly good results were obtained with nutrient media which contain a mixture of glucose, galactose and mannose for example in a mass ratio of 1:(0.5-3):(1-5) and in particular of 1:(0.7-2.4):(1.8-4.0) where each of the

carbohydrates is particularly preferably used in the D(+) form. The total concentration of all sugars during the fermentation is preferably in a range of 0.1 to 10 g/l, particularly preferably in a range of 2 to 6 g/l in the culture medium. The carbohydrate mixture is preferably added dependent on the respective requirement of the cells as elucidated in more detail in the following.

US Patent No. 6,673,575, col. 3, lines 4-20. In addition, the patent also discloses culturing cells in media containing either at least one carbohydrate or at least two carbohydrates. *See e.g.*, claims 1 and 4. Hence the disclosure includes a huge range of carbohydrates and combinations of carbohydrates that are encompassed within the terms “monosaccharides and disaccharides,” in addition to eleven specific carbohydrates recited. Directing attention only to these eleven, Applicant’s representative calculates that a total of 2047 different groups of from one to eleven carbohydrates are possible, using only these eleven carbohydrates to make the groups.<sup>1</sup> Adding to this already large number, the essentially incalculable number of compounds encompassed within “monosaccharides and disaccharides” would produce a very large genus of carbohydrates and groups of carbohydrates. The carbohydrates glucose, mannose, and galactose, and all possible combinations thereof (which would encompass seven possibilities), are given special notice, although data in the application includes only one such combination, that is, glucose, mannose, and galactose.

Applicant asserts that the rejected claims are nonobvious because the selection of a species is nonobvious over a reference, such as Franze et al., which discloses a broad genus. The current claims, like the formerly pending claims, are directed to media and methods for its use, wherein the media contain either: 1) fructose, galactose, mannose, and N-acetylmannosamine (claim 44 and claims dependent thereon); 2) galactose and N-acetylmannosamine (claim 55 and claims dependent thereon); 3) fructose, galactose, and mannose (claim 69 and claims dependent thereon); or 4) fructose and galactose (claim 81 and claims dependent thereon). Each

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<sup>1</sup> The number of combinations of  $n$  objects taken  $k$  at a time can be calculated using the formula:

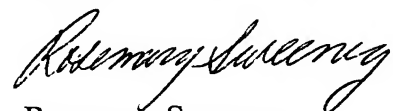
$\frac{n!}{k!(n-k)!}$ . Grossman and Turner, *Mathematics for the Biological Sciences*, p. 24-30, Macmillan Publishing Co., New York, Collier Macmillan Publishers, London, 1974.

of these independent claims recites one or more sugars from the list of eleven sugars recited in Franze et al. plus, in some cases, N-acetylmannosamine. Thus, each claim recites a selection from the genus of Franze et al., which, under *Baird*, constitutes a nonobvious selection from a broad genus. Further, none of the claims are directed to the preferred combination of Franze et al., i.e., glucose, mannose, and/or galactose. Thus, there is no suggestion to modify the broad disclosure of Franze et al. to arrive at the claimed combinations and no reasonable expectation that the claimed combinations would function to increase protein sialylation. Indeed, many of the combinations tested by Applicant (*see* Figure 2 and Example 1) did not, in fact, increase protein sialylation, illustrating that the lack of expectation of success on legal grounds is reflected in actual, experimental data showing that many combinations encompassed by the broad description of Franze et al. do not increase protein sialylation under the conditions used in the instant application.

### ***Conclusion***

Applicant believes all claims are in condition for allowance and respectfully requests notice to that effect. If the Examiner believes that any outstanding issues can be most easily dealt with via teleconference, he is invited to contact the undersigned at the direct dial telephone number listed below.

Respectfully submitted,



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